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Serum vitamin D status in pediatric critical care

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Abstract
Aim: Vitamin D deficiency (VDD) is a huge public health problem affecting people of all ages, races, and genders. Studies performed in pediatric intensive care units (PICUs) found a prevalence of VDD between 30% and 70%, and it was shown that VDD was related to a more severe disease course and a longer PICU stay. The aim of our study was to investigate the prevalence of VDD at PICU admission and its relationship between disease type, severity, and prognosis.
Material and Method: The medical records of pediatric patients aged 1 month-17 years who were admitted to PICU between March 2017 and March 2018 were retrospectively reviewed. The patients' pediatric mortality risk score (PRISM), 25-hydroxyvitamin D(25(OH)vitD) level at admission, serum calcium (Ca), phosphorus (P), magnesium (Mg), and alkaline phosphatase (ALP) levels were recorded. Blood 25(OH)VitD level ≤20 ng/mL was defined as VDD. Patients with low 25(OH)VitD levels (≤20 ng/mL) were grouped as 'Group-1', those without (>20 ng/mL) were grouped as 'Group-2'.
Results: Among the patients, 55 (56.7%) had VDD. The mean 25(OH)D level was 12.7 ng/ml in Group 1 and 27.8 ng/ml in Group 2. Patients in Group 1 had a greater age, body weight, and height, but BMI (body mass index) was not significantly different between both groups. The two groups also did not differ significantly with respect to race, gender, admission season, underlying disease, PRISM score, sepsis rate, vasoactive agent need, mechanical ventilation support, number of days on mechanical ventilation, number of days of PICU stay, and mortality rate.
Discussion: As the prevalence of VDD is high among pediatric critical care patients, it is important to perform screening and administer effective replacement therapy to these patients. We believe that assessment of the relationship between vitamin D and disease duration, severity, and prognosis, and determining optimal vitamin D dose, administration route, and safety profile through prospective controlled studies could affect morbidity and mortality rates.

Keywords
Vitamin D, Pediatric Intensive Care, Mortality, Illness Severity

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Introduction

VDD is a major public health problem affecting people of all ages, races, and genders. Previous studies have shown that VDD is endemic in both children and adults and is related to increased viral respiratory infections and sepsis [1,2]. A reduction in the incidence of influenza infections was observed among children receiving vitamin D replacement therapy [3]. It has been reported that the level of cathelicidin, an antimicrobial peptide, was lower particularly among adult patients with VDD suffering sepsis [4]. Studies conducted in PICUs revealed that the prevalence of VDD ranges between 30% and 70%, and VDD has been shown to correlate to a more severe disease course and a longer PICU stay [5-7].

Similar to the general population, most children with reduced consumption of certain foods and exposure to inadequate number of ultraviolet rays are also subject to vitamin D deficiency before disease onset. Critical disorders and some interventions (surgery, fluids, extracorporeal membrane oxygenation, cardiopulmonary bypass, plasma exchange) may markedly reduce 25(OH)D level. Hepatic, parathyroid, and organ dysfunctions (reduced hydroxylation) and increased tissue demand during catabolism, reduced endogenous production, and malabsorption due to intestinal edema also play a role in reduced 25(OH)D level [8].

Our study aimed to investigate the relationship between VDD's prevalence at PICU admission and its relationship with disease type, severity, and prognosis among critically ill pediatric patients.

Material and Methods

The medical records of pediatric patients aged 1 month-17 years who were admitted to Health Sciences University, Umraniye Training and Research Hospital, Pediatric Intensive Care Unit between March 2017 and March 2018 were retrospectively reviewed. Patients with rachitism, postoperative cardiac patients, patients with missing information, and patients that stayed at PICU for less than 24 hours were excluded. The patients' age (months), gender, admission diagnosis, underlying disorders, vasopressor need, septic status, intensive care unit stay, and days on mechanical ventilator were recorded. Pediatric mortality risk score (PRISM) calculated from the patients' data in the first 24 hours, serum 25(OH) D level measured at admission, and serum Ca, P, Mg, and ALP levels were recorded.

Prematurity is one of the important risk factors for vitamin D deficiency. Therefore, patients with a history of premature birth were excluded from the study. Vitamin D deficiency was defined as a 25(OH) D level < 20 ng/ml regardless of age group, therefore, patients were evaluated without subgrouping according to their age.

The 25(OH)D level was measured by the chemiluminescence method (Abbott Architect 2000). Serum 25(OH)D level ≤20 ng/mL was defined as VDD (7,8,17,18,). The patients were grouped into two according to the blood l 25(OH)D levels. Patients with low 25(OH)D levels (≤20 ng/mL) were termed as 'Group-1', and those without (>20 ng/mL) as 'Group-2'.

Sepsis was defined by the presence of systemic inflammatory response syndrome coupled with clinically or microbiologically documented infection. Statistical analyses in the study were carried out under three subtitles as descriptive, univariate, and multivariate analysis methods. Criteria of normal distribution were tested for numeric variables. Two independent study groups were compared using the Mann-Whitney U test and more than two independent groups using the Kruskal-Wallis test for non-normally distributed numeric variables. Categorical variables were compared with the Chi-square test between two independent groups. Multivariate analyses were carried out with Cox regression analysis for censored time-to-event data; a logistic regression model was used for dichotomized data structures used for mortality assessment; and multivariate linear regression analysis was used for assessment of quantitative vitamin D level. A two-sided hypothesis structure and a 5% Type-1 level of error were used for all statistical analyses. Data analyses were performed using the SPSS 21 (IBM Corp. in Armonk, NY, USA) software package.

This study was approved by Health Sciences University, Ümraniye Training and Research Hospital.

Results

Among the study population, 52 (53.6%) were females and 45 (46.4%) were males. The mean age of the study population was 58.2±39.1 months; the mean weight was 18.7±15.7 kg; the mean height was 98.0±32.4 cm; the median BMI was 16.6±3.7 (Table 1). The most common cause of PICU admission was acute respiratory failure (31, 32%), followed in descending order by neurological disorders (27, 27.8%) and infectious disorders (22, 22.7%); 37.1% of the patients had received vitamin D replacement.

Admissions most commonly occurred in fall (36.1%), followed in descending order by summer (25.8%), spring (23.7%), and winter (14.4%).

The incidence of sepsis was 66%; the rate of inotropic infusion was 21.6%; the proportion of patients receiving mechanical ventilation and respiratory support was 46.4%.

Among the patients, 87.6% were of Turkish nationality and 12.4% were foreigners. The mean duration of mechanical ventilation was 16.2±29.8 days; and the mean duration of intensive care unit stay was 15.8±23.8 days. Eighty-one (83.5%) patients were discharged and 16 (16.5%) patients were lost.

Group 1 had a mean 25(OH)D level of 12.7 ng/ml and Group

Table 1. Demographic properties and laboratory values of the study population

	Mean±SD	Min-Max
Age (months)	58.2 ± 39.1	(2-214)
BW(kg)	18.7 ± 15.7	(2.4-759)
Height (cm)	98.0 ± 32.4	(52.0-180)
BMI (kg/m^2)	16.6 ± 3.7	(7.7-28)
PRISM	13.9 ± 9.1	(1-38)
Ca (mg/dl)	9.1 ± 0.7	(7.2-11.3)
Ionized Ca (mmol/L)	1.2 ± 0.1	(0.9-1.5)
P (mg/dL)	4.3 ± 1.1	(1.2-6.7)
ALP (U/L)	158.2 ± 73.8	(43-476)
Mg (mg/dL)	2.0 ± 0.3	(1.4-2.8)
25(OH)D ng/mL	20.3 ± 10.9	(4.1-53)

BW: Body weight, BMI: Body mass index, PRISM: Pediatric risk of mortality score, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, Mg: Magnesium

Table 2. Comparison of patient groups by Vitamin D level

	Group 1 25(OH)D ≤20ng/mL		Group 2 25(OH)D >20ng/mL		p
Girl n, %	27	49.1	25	59.5	
Boy n, %	28	50.9	17	40.5	0.307
Age (months) mean	45		20		0.021
BW (kg) mean	16		10		0.003
Height (cm) mean	102		81.5		0.004
BMI (kg/m^2)	16.1		15.6		0.130
PRISM mean	13.8		14		0.906
Sepsis n, %	36	65.5	28	66.7	0.901
Need for inotropes n, %	11	20	10	23.8	0.652
Mechanical ventilation n, %	25	45.5	20	47.6	0.832
Duration of mechanical ventilation (days)	9		6.5		0.606
Duration of PICU stay (days)	7		9.5		0.242
Race (Turkish) n, %	46		39		0.172
Mortality n, %	10		6		0.608
Ca (mg/dl)	9.2		9		0.694
Ionized Ca (mmol/L)	1.2		1.2		0.519
P (mg/dl)	4.4		4.1		0.076
ALP (U/L)	145		165		0.057
Mg (mg/dL)	1.9		2		0.657

Table 3. Comparison of patient groups with respect to prognosis

Patient (n: 97)	Survived		Non-survived		p
Sepsis n, %	49	(76.6)	15	(23.4)	0.010
Vasoactive agent use n, %	8	(38.1)	13	(61.9)	<0.001
Mechanical ventilation n, %	30	(66.7)	15	(33.3)	<0.001
25(OH)D (ng/mL)	19.7		18.3		0.705
Duration of mechanical ventilation (days)	5		13.0		0.001
Duration of PICU stay (days)	7		14.5		0.011
PRISM score	11.3		26.9		<0.001
Ca (mg/dl)	9.2		8.8		0.028
P (mg/dl)	4.3		4.1		0.578
ALP (U/L)	163.2		132.8		0.133
Mg (mg/dL)	2.0		1.1		0.281

2 had a mean 25(OH)D level of 27.8 ng/ml. Group 1 had a greater age, body weight, and height (p:0.021, p:0.003, and p:0.004, respectively). There was no significant difference with respect to BMI (p:0.130). The two groups showed no significant differences in race, sex, admission season, underlying disorder, PRISM score, sepsis rate, need for inotropic infusion, MV support, number of days of PICU stay, number of days of MV support, and mortality rate. Similarly, laboratory values were also similar between the two groups (p<0.05) (Table 2).

The patients were compared with respect to prognosis; significant differences were found with regard to sepsis status, need for inotropic infusion, need for respiratory support with MV, number of MV days, number of PICU days, PRISM score, and serum calcium level; however, there were no significant differences in 25(OH)D levels and other laboratory values (Table 3).

Discussion

In studies performed in pediatric intensive care units, the prevalence of VDD has been reported to be 30% to 70%. In a study from Turkey conducted by Aşılıoğlu et al [9], which comprised 205 pediatric intensive care unit patients, the prevalence of VDD was 58.5%. That study also reported that multivariate analysis revealed a significant correlation only between patient age and winter season; it also revealed that patients with VDD were older, heavier, and had a greater rate of vasopressor need, but both groups were similar with respect to PRISM score and mortality rate. In a study by Elmoneim et al [10], which was performed among pediatric critical care patients, a correlation was found between 25(OH)D level and duration of intensive care unit stay and number of days on mechanical ventilator, but no correlation existed between mortality and 25(OH)D level. We found a VDD prevalence of 56.7%. Similar to that study, we found no significant difference between the study groups with respect to duration of PICU and hospital stay, MV need, PRISM score, and mortality rate. Unlike that study, there was no correlation between VDD prevalence and seasons; the two groups showed no significant difference in vasoactive agent use.

In a large-scale pediatric trial, it was reported that VDD was more prevalent among overweight children than in slim peers[11]. In our study, the mean body weight of patients with VDD was significantly lower than that of patients with a normal 25(OH)D level. This stemmed from a lower mean age of patients with VDD.

In a study comprising 101 critically ill pediatric patients, it was shown that patients with VDD had a higher mean age and a greater need for ventilator and vasoactive agent need. Multivariate analysis showed a correlation between VDD and duration of PICU stay, prism and pelod score, fluid bolus and ventilation need, vasoactive agent use, and mortality [12]. Unlike literature data, our study did not show any correlation with the presence of sepsis, vasoactive agent needs, mechanical ventilation needs, the number of days on mechanical ventilation, the number of days at intensive care unit, and mortality. These differences were attributed to variations of study groups, sunlight exposure, diet, climate, and the status of vitamin D replacement, as well as genotype variations of proteins involved in vitamin D transport, metabolism, and function.

In a study performed in 2016 at PICU, VDD prevalence was reported as 57%. Patients with VDD were younger, mostly male, and had more prominent renal dysfunction. VDD prevalence was also higher among patients admitted for cardiopulmonary disease [10]. Our study similarly showed that patients with VDD were younger, but the two groups did not differ significantly with respect to gender distribution. As we did expect lower 25(OH) D level among patients undergoing cardiovascular surgery, we excluded such patients.

Hebber et al [13] compared 61 PICU patients and 46 control subjects. They reported that 60% of PICU patients had VDD; on the other hand, the corresponding rate among the control subjects was 30%. They also reported that there was no correlation between 25(OH)D level and disease score (prism, pelod), and added that patients with asthma had a 25(OH)D level of 16.9 ng/mL, while those without it had a 25(OH)D level

of 18.7 ng/mL. While 50% of patients admitted in the fall and winter had VDD, those admitted in spring and summer had a prevalence of 30% (p:0.003). Our study revealed that the VDD prevalence was 53% among patients admitted in the fall and winter, and 50% in those admitted in the spring and summer, showing no statistical significance.

Another study reported from Canada showed a significant difference between 25(OH)D levels at ward and PICU admission and that found at discharge (72 nmol/L and 49 nmol/L) [14]. In an adult population, Yi et al. [15] similarly reported a reduction in 25(OH)D level at 10- and 35-days periods.

Another study published in 2014 found a 25(OH)D level of 11.7 ng/mL among critically ill pediatric patients. In 71.4% of the patients, 25(OH)D level was low, in 46.2% of patients there was hypocalcemia, and 61.2% had elevated ALP level. No change was observed in 25(OH)D levels during patients' hospital stay. No correlation was found between the PIM 2 score and 25(OH)D level, and no significant difference was evident between 25(OH) D levels of survivors and deceased ones [16]. Our study revealed a 25(OH)D level of 20.3 ng/ml, and 56.7% of the patients had a low 25(OH)D level. Both groups showed no significant differences in serum calcium, ionized calcium, phosphorus, and alkaline phosphatase levels. However, we showed that each unit of increase in the P level increased VDD prevalence by 1.54 times, while each unit of increase in the ALP level decreased VDD prevalence by 0.1%.

McNally et al. [11], in a multicenter study conducted in Canada, reported that the level of a 25(OH)D level was 67-75 nmol/L among healthy children and 43 nmol/L among critically ill children. They also reported that 25(OH)D level was lower among patients who needed a catecholamine infusion, had hypocalcemia, received fluid resuscitation in excess of 40 ml/kg, and needed mechanical ventilation. The authors stated that acute reduction of 25(OH)D level was physiologically more prominent than chronic reduction, which occurred due to affection of compensatory mechanisms by inflammation and multiorgan dysfunction during the critical disease process. Another study reported in 2013 by the same author revealed that pediatric patients undergoing cardiopulmonary bypass had a mean preoperative 25(OH)D level of 60 nmol/L, with 42% having VDD; in the postoperative period, the mean 25(OH)D level was reduced to 35 nmol/L, while the prevalence of VDD increased to 84% [17]. Low postoperative 25(OH)D level was correlated to increased catecholamine need, fluid need, and longer duration of mechanical ventilation. The marked reduction in 25(OH)D among patients undergoing elective cardiac surgery was attributed to dilution secondary to volume expansion [18]. We linked the lack of correlation between catecholamine need, duration of mechanical ventilation, and 25(OH)D level to the exclusion of patients undergoing cardiovascular surgery.

Another study performed in 2016 at PICU in Spain found a VDD prevalence of 43.8% and a mean 25(OH)D level of 22.28 nm/mL. The patients with VDD had a higher mean age, PRISM score, morbidity rate, and patent educational level; they had more common admissions in the spring and winter; they also had a longer PICU stay. The authors reported that VDD increased morbidity by a factor of 5.4 [19].

Saboktakin et al. [20], in 2016 investigated vitamin D status among critically ill children. They administered 300.000 U vitamin D IM to patients with VDD and designated the patients with normal 25(OH)D level as a control group. They compared groups with and without vitamin D replacement. The control group had a longer duration at intensive care, mechanical ventilation, and a greater need for vasoactive agent use; however, study group had higher mortality. The authors reported that an adequate level of increase in 25(OH)D level could not be attained despite vitamin D replacement during hospitalization, especially for deceased patients.

Cechi et al. [21], in a study of 170 adult patients with sepsis, septic shock, and trauma, found that 25(OH)D level was lower in the sepsis group (p<0.001); mortality was higher in the sepsis group, but there was no correlation between 25(OH)D level and mortality. Ponnarmeni et al. [22] reported a lower 25(OH)D level among critically ill pediatric patients with sepsis compared with healthy controls (49.25 vs 68.7 nmol/L).

Vitamin D plays an important role for the induction of antimicrobial response against pathogens in humans. Among individuals with VDD, it has been shown that macrophages could not attain optimal regulation of cathelicidin protein (LL-37) production, and vitamin D replacement improved LL-37 response to infectious signals [23]. Jeng et al. [24] showed a positive correlation between 25(OH)D level and plasma LL-37. However, in a similar study conducted in 2012, 25(OH)D level and disease score showed no significant correlation; VDD risk was greater in asthmatic patients [25].

In conclusion, VDD prevalence is higher among critically ill pediatric patients. Since the role of vitamin D in bone development and immunity is known, it is important to screen critically ill children and prescribe an effective replacement. We believe that assessment of the relationship between vitamin D and disease duration, severity, and prognosis and determining optimal vitamin D dose, administration route, and safety profile through prospective controlled studies could affect morbidity and mortality rates.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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